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EXAMINER	
LEAVITT, MARIA GOMEZ	
ART UNIT	**PAPER NUMBER**
1633	

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10/19/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/579,988	LEONARD ET AL.	
	Examiner	Art Unit	
	Maria Leavitt	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-31* is/are pending in the application.

4a) Of the above claim(s) *6,8,13-17 and 21-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,7,9-12 and 18-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05-19-06,08-08-06,05-31-07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Notice to Comply	Application No. 10/579,988	Applicant(s) LEONARD ET AL.	
	Examiner Maria Leavitt	Art Unit 1633	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e). The correct SEQ ID NO:2 is present in the paper copy of the of the sequence listing only. Therefore a search of the correct sequence is not possible.

☒ 7. Other: In this instance, at page 19, line 20 of the specification discloses the following amino acid sequence, "WSXWS" that is not identified by sequence identification number. Furthermore, this sequence does not appear in the sequence listing as filed.

Applicant is required to submit the following:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application**.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216 or (703) 308-2923
For CRF Submission Help, call (703) 308-4212 or 308-2923
PatentIn Software Program Support
Technical Assistance.....703-287-0200
To Purchase PatentIn Software.....703-306-2600

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR REPLY

DETAILED ACTION

Applicant's election of 08/02/2007 **with traverse** in response to the restriction requirements filed on 07-11-2007 has been acknowledged. Applicant election Group II, i.e., claims 5, 7, 9-12 and 18-20 is acknowledged. Applicant's election of species "a viral antigen" from among the antigens listed in claim 11 is acknowledged. Claims 6, 8, 13-17 and 21–31 are withdrawn from further consideration pursuant to 37CFR 1.142(b) as being drawn to nonelected inventions.

Response to remarks

Applicant's Arguments of 08/02/2007 in view of the official restriction/ election of species requirement for elected Group II have been respectfully reconsidered but are not found to be persuasive.

On page 2 of Remarks, Applicants contend that the office has failed to meet the criteria for a proper restriction and election of species by arguing that claims of Groups I and II encompass the administration of IL-21 or an agonist thereof and the search of these groups would uncover references that overlap. Moreover, Applicants note that at least claims 5 and 20 links the subject matter between the claims of Groups I and II and each of the claims of these Groups I and II depends directly or indirectly on claims 5 or 13, and as such the requirement for restriction is not proper. Such is not persuasive.

Contrary to applicant assertion, all of the claimed inventions are not linked so as to form a single general inventive concept for the reasons set forth in the Office action mailed on July 11,

2007 and the following reasons. Specifically, the inventions of Groups I and II are drawn to *in vivo* and *ex vivo* methods of enhancing an immune response. Thus the special technical feature of the invention of claim 5 as part of Group I is drawn to a method for *in vivo* induction of an immune response in a subject by contacting the cell with a composition comprising IL-21 e.g., by intravenous injection, whereas the special technical feature of the invention of claim 5 as part of Group II is drawn to a an *ex vivo* method of induction of an immune response in a subject by contacting the population of cell with a composition comprising IL-21 which require the step of isolating said population from a subject before culture with IL-21. Thus the inventions are materially different processes comprising distinct process steps, which therefore necessarily induce differenciation into a memory B cell and a plasma cell by different modes of action or effect, so as to lack unity of invention and form a single general inventive concept. Moreover, the examiner notices that restriction of individual claims into separate groups is governed by PCT Rule 13, notably, PCT Rule 13.3, which states that:

> The determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim.

On page 3 of Remarks, Applicant argue that the search for a particular species from among viral antigens, bacterial antigens, and parasite antigens (Group II) or JAK1, JAK3, STAT5A, and STAT5B (Group V) likely would uncover references that would be considered by the Office during the examination of the other species within the group, as such Applicants contend that the requirement for election of species is not proper. Such is not persuasive.

As stated in the previous office action the species are independent or distinct because there are methods comprising **antigenic molecules** having different chemical structures, physical properties, and biological functions as a result of containing different chemical compounds or expressed genes. Thus, the combined features of a particular species, distinct structurally and functionally, would not necessarily overlap with one another when a prior art search is conducted. As a result the search and examination beyond one specific species will impose a serious burden in the examiner.

Therefore, for these reasons and the reasons set forth in the Office action mailed July 11, 2007, these inventions do not share unity of invention as required under PCT Rule 13 and the restriction/election requirement is still deemed proper and is therefore made FINAL.

Therefore new claims 5, 7, 9-12 and 18-20 are currently being examined to the following grounds of rejection are applicable.

Specification

The disclosure is objected to for the following reason: The specification contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). Sequences appearing in the specification and/or drawings must be identified by sequence identifier in accordance with 37 C.F.R. 1.821(d). According to 37 CFR § 1.821(a), an unbranched sequence of four or more specifically identified amino acids or an unbranched sequence of ten or more nucleotides must be identified by sequence identification numbers. See MPEP § 2422.01.

In this instance, at page 19, line 20, the specification discloses the following amino acid sequence, "WSXWS" that is not identified by sequence identification number. Therefore, since this amino acid sequence contains an unbranched sequence with four specifically identified amino acids, it requires a sequence identification number pursuant to 37 CFR § 1.821(a). Notably, this sequence also does not appear in the sequence listing as filed.

As noted in the attached Notice to Comply, appropriate action correcting this deficiency is required. If necessary to correct the deficiency, Applicant must submit paper and computer-readable copies of a substitute sequence listing, together with an amendment directing its entry into the specification and a statement that the content of both copies are the same and, where applicable, include no new matter.

Claim Rejections - 35 USC § 112 - written description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 5 and dependent claims 7, 9-12 and 18-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to any person skilled in the art to which it pertains, or with which it is most nearly connected, at the time the application was filed, that the inventor, at the time the application was filed, had possession of the claimed invention.

Claims 5, when given the broadest reasonable interpretation, encompass a genus of IL-21 polypeptides and Il-21 agonists including variants or fragments of such composition , able to contact a population of cells comprising a mature B cell and a B cell progenitor cell so as to induce differentiation of said B cells into a memory B cell and a plasma cell, respectively, to enhance an immune response against a viral epitope when introduced into a subject. However, the written description in this case only sets forth one species of polypeptide sequence, i.e., a human IL-21 (100 ng/ml, R&D sytems, Minneapolis, MN). (page 44, line 25). The specification discloses in Example 4 the effect of IL-21 on human isolated B cells, from direct stimulation of B cells with IL-21, in the presence of anti-CD40, in combination with either IL-4, anti-CD40, or both stimuli (p. 53, lines 10-15). FACS analysis teach that B cells contacted with IL-21, in the presence of anti-CD40, in combination with either IL-4, anti-CD40, or both stimuli resulted in IL-21 induced expression of sydecan-1 (a plasma marker) and induced expression of surface IgG (Fig. 6B and Fig. 6C), which overall indicates that IL-21 " induces an increase in immature B cells, alters the B cell phenotype and is a potent inducer of B cell maturation to memory B/post-switch cells and plasma cells. IL-21 also induces differentiation of human B cells into plasma cells (FIG. 8) and memory B cells(p. 53, lines 23-26). Moreover, the specification discloses at pages 30-34, that "IL-21 polypeptides (including variant polypeptides and IL-21 polypeptide analogs, such as IL-21 agonists), can be composed of amino acids joined to each other by peptide bonds or modified peptide bonds, can contain amino acids other than the 20 gene-encoded amino acids, contain alterations which produce silent substitutions, additions, or deletions, and others (p. 30, lines 10-31; p. 31, lines 1-13).

Thus, the claims are broadly, but reasonably interpreted as encompassing an extremely large genus of structurally and functionally diverse IL-21 polypeptides able to decrease the number of mature B cells, but increasing immature cells and driving differentiation of post-switch cells upon contact with a population comprising a mature B cell and a B cell progenitor cell.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude that the inventor(s) had possession of the claimed invention. Such possession may be demonstrated by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to practice, showing that the invention was "ready for patenting", or by describing distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention (January 5, 2001 Fed. Reg., Vol. 66, No. 4, pp. 1099-11). Moreover, MPEP 2163 states:

> [A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.

Overall, what these statements indicate is that the Applicant must provide adequate description of such core structure and function related to that core structure such that one skilled in the art could determine the desired effect. Hence, the analysis below demonstrates that Applicant has not determined the core structure for full scope of the claimed genera.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, Applicant, provides one example of IL-21 protein i.e., a human IL-21 (100 ng/ml, R&D systems, Minneapolis, MN). . Thus the specification provides sufficient description for the human IL-21 (100 ng/ml, R&D systems, Minneapolis, MN). . However, the description of one human IL-21 that induces maturation of B cells accompanied by class switching and plasma formation *in vitro*, is not representative of the entire **genus of IL-21 or unspecified IL-21 agonists thereof** because the genus is highly variable, inclusive to a variety of structurally undefined compositions comprising IL-21, e.g., polynucleotides that also are functionally diverse beyond their requirement of promoting maturation of B cells accompanied by class switching and plasma formation (p. 52, lines 16-17). Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. For example, a search of "IL-21" in the protein database available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Protein, conducted on October 2, 2007 provided 95 possible IL-21 proteins and it is unclear to which one(s) the claim refer. At the time the invention was made, it was well known in the art that certain positions in the sequences of peptides/proteins are critical to the protein's structure/function relationship, particularly, various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. Particular regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (Guo et al.,.Proc Natl Acad Sci U S A. 2004 101:9205-10; p. 9209, col. 1, last paragraph). The skilled artisan understands that one nucleotide change in a

DNA molecule or one amino acid change in the polypeptide encoded by the DNA molecule could result in the loss of its biological activity as demonstrated in the generation of sickle-cell anemia wherein on specific amino acid mutation gave rise to the inherited disease (Biochemistry, John Wiley and Sons, 1990, p. 126-129). Even single-nucleotide polymorphism without affecting the amino acid sequence can affect folding of the protein and thus alter its function (Kimchi-Sarfaty et al., 2007, Science, pp. 525-528; p. 527, col. 3, last paragraph). Since, the relationship between a sequence of a peptide and its tertiary structure is not well understood and is not predictable, the disclosure provided is not deemed to be descriptive of the complete structure of a representative number of species encompassed by the claims as one of skill in the art cannot envision a genus of IL-21 and unspecified IL-21 agonists thereof having the ability to induce differentiation of a mature B cell and a B cell progenitor cell into a memory B cell and a plasma cell, respectively, so as to enhance the immune response against a viral antigen. There is no structure/function relationship taught at all for a genus of IL-21 or unspecified agonists of IL-21. The specification does not teach which regions or domains of the IL-2 are essential for said activity. There is no disclosure of what amino acids are in the active site, the binding pocket or the hydrophobic core of the protein. There is no teaching of how many amino acids may be deleted from either or both the N- and C-terminals and retain function.

Next then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e., induces maturation of B cells accompanied by class switching and plasma formation when injected into mice), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, there are not other disclosed characteristics in addition to the functional one

discussed above. Such functional characteristic, however, do not allow one of skill in the art to distinguish the different members of the genera form each other.

Applicant's attention is directed to *In re Shokal*, 113 USPQ 283 (CCPA 1957), wherein it is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 CCPA (Patents) 1309, 97 F2d 623, 38 USPQ 189; *In re Wahlforss*, 28 CCPA (Patents) 867, 117 F2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of **a composition comprising a genus of IL-21 or unspecified IL-21 agonists thereof** having the ability to induce differentiation of a mature B cell and a B cell progenitor cell into a memory B cell and a plasma cell, respectively, at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

Claim Rejections - 35 USC § 112 - enablement

To the extend that the claims read on an *ex vivo* method for enhancing an immune response in a subject, the following rejection apply.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 5 and dependent claims 7, 9-12 and 18-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not reasonably provide enablement for claims directed to an *ex vivo* method of enhancing an immune response to a viral antigen by introducing *ex vivo* differentiated memory B cells and a plasma cells obtained from a mature B cell and a B cell progenitor cell, respectively, after *in vitro* contact of said mature B cell and B cell progenitor cell with a genus of **IL-21 or unspecified IL-21 agonists**.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The specification does not reasonably provide enablement for claims directed to a composition comprising a genus of IL-21 or unspecified IL-21 agonists. Moreover, the

specification does not reasonably provide enablement for using *ex vivo* methods of therapy by introducing host cells exposed *ex vivo* to Il-21 into the body of a subject , so as to achieve an immune response against an intracellular viral pathogen, as the specification provide insufficient guidance for issues related to treatment of viral infection, issues related to autologous, allogeneic and xenogeneic transplantation so as to enhance an immune response against a viral antigen. Thus, the specification provides insufficient data to enable claims directed to the method as broadly claimed. Thereby, specific issues including differentiation of a mature B cell and a B cell progenitor cell into a memory B cell and a plasma cell after contact with **IL-21 or an agonist thereof**, immune responses against intracellular pathogens such as viruses and transplantation of a memory B cell and a plasma cell to a discordant or concordant animal species, have to be examined and considered for patentability regarding the broadly claimed methods.

The instant claims are drawn to a method for enhancing an immune response against a viral antigen by contacting a cell population with an IL-21 protein, which exhibits the ability to induce differentiation of a mature B cell and a B cell progenitor cell into a memory B cell and a plasma cell, respectively. It is noticed that the only *in vivo* example provided in the specification teaches direct administration to mice of a vector comprising a gene encoding IL-21 and not ex vivo therapy comprising exposing B cells exogenously to IL-21 and introducing the transformed cells into a subject. It is also noticed that if Applicants intend to introduce the limitation of contacting a population of B cell with a nucleic acid encoding IL-21 rather than Il-21, the claims will require a further restriction.

In Examples 2 and 4, the specification teach proliferation of isolated human B cell by culturing purified B cells with combinations of anti-CD40, anti IgM+IL-4 or LPS. Results teach,

for example, that IL-21 could induce apoptosis of anti-CD40 stimulated B cells, even though it augmented proliferation of anti-CD40 stimulated B cells (p. 49, lines 5-7). Moreover, the specification teaches at page 50, lines 26-28, that IL-21 potentially decreases expression of DC23 on naive B cells and also on B cells stimulated with LPS or anti-CD40. Particularly Example 4 teaches the effect of IL-21 on B cell maturation, from direct stimulation of B cells by IL-21, in the presence of anti-CD40, in combination with either IL-4, anti-CD40, or both stimuli (p. 53, lines 10-15). FACS analysis of B cells after contact with IL-21, in the presence of anti-CD40, in combination with either IL-4, anti-CD40, or both stimuli, show IL-21 induced expression of sydecan-1 (a plasma marker) and induced expression of surface IgG (Fig. 6B and Fig. 6C), which overall indicates that IL-21 " induces an increase in immature B cells, alters the B cell phenotype, and is a potent inducer of B cell maturation to memory B/post-switch cells and plasma cells. IL-21 also induces differentiation of human B cells into plasma cells (FIG. 8) and memory B cells" (p. 53, lines 23-26). In relation to the *in vivo* effects of IL-21 on B cell, the specification discloses that mice injected with IL-21 DNA exhibit a dramatic increase in the $IgD^{low}IgM^{low}$ population of $AA4.1^{low}$ splenocytes, which represent cells that have undergone Ig class switch recombination. Moreover, $AA4.1^{low}$ splenocytes, which include both, resting mature B cells and post switch cells, show that mature B cells were diminished based on the decrease in IgD^{+} cells, whereas and post switch cells (IgD^{-}) were markedly increased (p. 50, lines 1-12).However, the specification is silent about enhancing an immune response in a subject against a viral antigen, e.g., introducing or reintroducing *ex vivo* modified host cells into the body, so as to achieve an immune response against intracellular viral pathogens

In relation to the use of a composition comprising a genus of IL-21 or unspecified IL-21

agonists, the claims are considered broad because the claims do not define the functional limitation of any IL-21 protein or undefined analogs having the ability to induce differentiation of a mature B cell and a B cell progenitor cell into a memory B cell and a plasma cell, respectively. The application provides sufficient guidance for the use of a human IL-21 (100 ng/ml, R&D systems, Minneapolis, MN) (p. 44, line 25). However, the application is silent about a genus of IL-1 and analogs of IL-21 including variants or fragments of such IL-2 polypeptide able to exhibit the claimed functionality (e.g., contact with a population of cells comprising a mature B cell and a B cell progenitor cell to induce differentiation of said B cells into a memory B cell and a plasma cell, respectively, so as to enhance an immune response against a viral antigen when introduced into a subject). The art teaches a divergent number of IL-21 molecules, for example, a search of "IL-21" in the protein database available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Protein, conducted on October 2, 2007 provided 95 possible IL-21 proteins The specification does not teach regions or domains of the protein essential for the claimed activity. There is no disclosure of what amino acids are in the active site, the binding pocket or the hydrophobic core of the protein. The skilled artisan understands that one amino acid change in the polypeptide results in the loss of its biological activity as demonstrated in the generation of sickle-cell anemia wherein on specific amino acid mutation gave rise to the inherited disease (Biochemistry, John Wiley and Sons, 1990, p. 126-129). Since, the relationship between a sequence of a peptide and its tertiary structure is not well understood and is not predictable, it would required undue experimentation for one skilled in the art to determine alternative sequences meeting the claim requirements to induce differentiation of a mature B cell and a B cell progenitor cell into a memory B cell and a plasma cell, respectively,

so as to enhance an immune response against a viral antigen in an ex vivo method As set forth above by the nature of the invention, neither the prior art of record nor the as-filed specification provides sufficient guidance to enable a person skilled in the art to employ a genus of **IL-21 or IL-21 agonists** in an *ex vivo* method as broadly claimed.

In relation to enhancing an immune response against a viral antigen, the art teaches that humoral immunity (e.g. Ab production) is effective specifically for extracellular pathogens and antigens (e.g., gram positive bacteria, toxins). However, viruses are intracellular pathogens (grow inside cells of the host). When viruses are inside cells they are not accessible to Ab, only when they are outside in the body fluids they areexposed to antibodies. Therefore, the immune system responds to intracellular viruses to induce an immune response against them by engaging both humoral and cellular immune responses. Moreover, generation of CD8+T cytotoxic cell, involved in cell-mediated immunity, is critical for immune responses against intracellular viruses (Immunology Lectures notes, 2002, School of Medicine USUHS, pp. 113-122). The art of record also discloses a divergent number of microbial infections with different antigenic properties as shown by their mechanism of depressing the immune responses in a subject (Mims et al., Medical Microbiology, 2004; pp 172-177). Moreover, the art teaches that interaction between CD40 and CD40L during T and B cell contact is essential for all events in thymus-dependent antigen responses such as Ig production, isotype switching, somatic hypermutation and induction of B cell memory (Lee et al., Proc Natl Acad Sci 1999:9136-41; p. 9136, col. 1). The specification discloses the effect of IL-21 on *in vitro* B cell maturation, from direct stimulation of B cells by IL-21, in the presence of anti-CD40, in combination with either IL-4, anti-CD40, or both stimuli (p. 53, lines 10-15). These responses lead to antibodies production by B cell, which

ultimately recognize native, soluble antigens. However, viral antigens are also processed on the surface of host cells in association with MHC I molecules eliciting a cell mediated immune response. Thus both B cell and T cells are involved in the immune response against a viral antigen. The instant claims broadly embrace a method for enhancing an immune response against a viral antigen that merely requires contacting a population of mature B cells and B cell progenitor with IL-21 without exposure to a viral antigen which are able when introduced in a subject to enhance the response against a viral antigen . However, the art teaches that humoral responses are not effective against intracellular pathogens but only against pathogens that are in extracellular fluids. Thus, it is not apparent how one skilled in the art would reasonably believe, without any undue experimentation, that introducing into a subject a differentiated population of a memory B cell and plasma cell that merely neutralizes extracellular pathogens, would effectively treat or enhance an immune response against any intracellular viral antigen specific to the viral infection to be treated without co exposure of said B cell population to a viral antigen, particularly given the interaction of both B and T cells immune responses as taught by the art ,and the lack of working examples for an *ex vivo* method as broadly claimed.

It is noticed that post-filing art only discloses *ex vivo* therapy methods in relation to enhancement on tumor-specific $CD8^+$T cell responses by IL-21 and not IL-21 enhancement of B-cells against a viral antigen. For example, post-filing art of Moroz et al., (2004, J. Of Immunology, pp.900-909), the anti-tumor activity of IL-21 injected i.p. using *ex vivo* therapy methods in mice injected through the tail vein with $3x10^6$ cells $CD8^+$T cells and challenged one day latter with syngeneic E.G7 thyoma tumor cells. The anti-tumor activity of IL-21 correlates with the accumulation of tumor-specific $CD8^+$T cells that possessed increased cytolytic activity

and that persisted in lymphoid tissues for several weeks (p. 901, col. 1, paragraphs 1 and 2). The author teaches that elimination of these cells (e.g., tumor-specific $CD8^+$T cells) abrogates mouse survival and abolished the induction of memory by IL-21 as measure by the ability to reject subsequent challenges (Moroz et al., 2004, J. of Immunology, p. 907; Sivkumar et al., Immunology, 2004, pp117-182; p. 180, col. 2, last paragraph).

Regarding the claimed invention drawn to the use of any type of population of a memory B cell and plasma cell, *e.g.*, autologous or non-autologous population of cells, applicant's claims as written encompass methods employing autologous, allogeneic and xenogeneic transplantation of nearly any non-irradiated population of cells type from any mammal to any other mammal, including transplants form dolphins or squirrels into human or vice versa. Transplanted population of cells from any subject to any other subject may not be truly syngeneic with their host mammal. Any such transplantation into immunocompetent hosts would result in a strong rejection response, which would ultimately destroy the host. Thus, the specification gives no guidance as to how to control such immune responses in any mammal if a claimed memory B cell and plasma cell is used. Even with the use of autologous genetically modified cells expressing a bioactive molecule, Riddell *et al.* (Nature Medicine, Vol. 2, 2:216-223, 1996) indicate that one unexpected insight from these studies was the ability of HIV-infected patients to induce strong primary T-cell immune responses to foreign antigens expressed by transferred autologous cytotoxic $CD8^+$ T cells (p. 221, column 1), and that "the rejection of genetically modified cells by these immunocompromised hosts suggests that strategies to render gene-modified cells less susceptible to host immune surveillance will be required for successful gene therapy of immunocompetent hosts" (abstract). Likewise, Vogelsang et al., (1994, Blood, p.

2061, paragraph 1 and abstract) teach that even autologous and allogeneic recognition by the host results in T-cell activation and graft disease, even in the case of allogeneic bone marrow transplantation. The specification discloses that administration to a subject of a therapeutically effective dose of a pharmaceutical composition containing nucleic acid encoding IL-21, an IL-21 polypeptide or an IL-21 agonist, can be included in a pharmaceutically acceptable carrier. However the specification is silent in relation to how to introduce a memory B cell and plasma cell to a discordant or concordant animal species. Thus, where *ex vivo* gene therapy using any memory B cell and plasma cell is not predictable in establishing a therapeutic outcome (*e.g.*, clinical efficacy) of gene therapy, the gene therapy methods referred to in the present claims are also not predictable, nor is it apparent how the enhancement of an immune response by introducing a memory B cell and plasma cell using applicant's claimed invention is reasonably correlated to a therapeutic immune effect in a human subject.

Finally, it appears that there are fundamental differences in murine B cell development when compared to human B cell development, so it would be highly unpredictable if IL-21 or analogs thereof (e.g., fragments or variants) from one species (e.g., mice) would induce differentiation of a mature B cell and a B cell progenitor cell into a memory B cell and a plasma cells from another species (e.g., human) or even if a human IL-21 would induce differentiation human mature B cells and B cell progenitor cells. For example, Ozaki et al (2002 Nature 1630-1634) teach that IL-21 exhibits different functionality in differentiation of human B cells that it does in mouse B cells and that one explanation for this difference in B cell response to IL-21 is that IL-7 is vital for B cells in laboratory mice whereas in humans IL-7 signaling can be inactivated without loss of B cell development (p. 1633, column 3). The as filed specification

provides one *in vivo* example teaching direct administration to mice of a vector comprising a gene encoding IL-21, which cannot correlate with and *ex vivo* method in a human subject as broadly claimed. Thus, one of skill in the art would not conclude that results obtained in a mouse system using IL-21 would extrapolate to using any IL-21, fragments or variants to enhance an immune response against a viral antigen in a human subject and would have to practice undue experimentation to practice the invention commensurate in scope with the claims.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Conclusion

Claims 5, 7, 9-12 and 18-20 are rejected

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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